deliveries could be reduced significantly from 1956 levels without interfering with the ability of cigarettes to satisfy smokers' addiction and to provide other desired pharmacological effects of nicotine.

Once nicotine deliveries neared the minimum thresholds identified by the cigarette manufacturers, however, the manufacturers reversed course and began to enhance nicotine deliveries. As the tobacco industry documents in the record indicate, the industry feared that at these low levels, cigarettes might not deliver sufficient nicotine to smokers. *See* section II.C.3., above. Consequently, the cigarette manufacturers began to take measures to raise nicotine deliveries, such as using nicotine-rich tobacco blends in ultra-low tar cigarettes. *See* section II.C.4., above. The trend of increasing nicotine deliveries since 1982 reflects these actions.

Moreover, the Agency disagrees with the manufacturers that efforts to enhance nicotine deliveries will necessarily be reflected in the nicotine deliveries measured by smoking machines. To the contrary, the evidence in the record indicates that some of the methods used by the cigarette manufacturers to enhance nicotine deliveries are *not* reflected in the measured nicotine deliveries. The use of "elasticity" technologies, such as ventilation systems that can be blocked by smokers, is one example. As described in section II.C.4.b, these technologies are designed to allow smokers to inhale more nicotine than would be measured by a smoking machine. Similarly, the use of ammonia technologies to liberate "free" nicotine, which is described in section II.C.4.c., has effects

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BATCO and Philip Morris researchers reached similar conclusions. According to one BATCO research study, a smoker's "nicotine requirement" is "about 0.8 mg per cigarette." Notes on the BATCO Group R&D Conference at Duck Key, FL (Jan. 12-18, 1974), at 2. *See* AR (Vol. 25 Ref. 327). Likewise, Philip Morris researchers recognized that "[t]he physiological response to nicotine can readily be elicited by cigarettes delivering in the range of 1 mg of nicotine." Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 4. *See* AR (Vol. 12 Ref. 133).

on nicotine absorption that are not reflected in the nicotine levels measured by a smoking machine.

2. The cigarette industry criticizes various aspects of FDA's methodology in calculating nicotine deliveries. The industry's comments assert that these alleged methodological problems make FDA's findings of increased nicotine deliveries unreliable.

The Agency disagrees with these comments. The industry itself acknowledges in its comments that nicotine deliveries have increased among the lowest-tar cigarettes.[948] This acknowledgment renders most of the industry's specific methodological objections irrelevant because it confirms the Agency's finding that nicotine deliveries have increased in the ultra-low-delivery category.

Moreover, the specific methodological comments of the cigarette industry are not well founded, as discussed below.

First, the cigarette industry is mistaken when it argues that FDA chose to use 1982 as its reference year to distort the trends in nicotine deliveries. FDA did not calculate these deliveries. Rather, these figures were calculated by the Federal Trade Commission (FTC), which annually reports tar and nicotine data for cigarettes. The FTC began its analysis in 1982 because this was the first year in which computer-readable data was available in the FTC files.

Second, the cigarette industry is mistaken when it suggests that the FTC did not follow the approach recommended by the Surgeon General for calculating sales-weighted tar and nicotine deliveries. In fact, the FTC followed this approach.

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[948] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. III, at 206. *See* AR (Vol. 535 Ref. 96).

II.C.6.

Third, FDA disagrees that brand shifting accounts for the increase in nicotine deliveries observed in the data. Brand shifting is unlikely to significantly affect reported average deliveries because brand shifts can occur in both directions (and so tend to cancel each other out) and because no single variety of cigarettes has a sufficient proportion of the sales to affect category averages.

Moreover, the data are inconsistent with the industry's brand-shifting theory. The data show that tar deliveries have either declined slightly (high- and low-tar categories) or increased slightly (ultra-low-tar category), while nicotine deliveries have increased significantly in these categories. If brand shifting was in fact causing the rise in nicotine deliveries in the three categories, tar deliveries should have risen similarly, which they did not. Most significantly, brand shifting cannot explain the increase in nicotine deliveries that was observed when all brands (from all three categories) were averaged together.

Fourth, FDA disagrees that normal analytical variation explains the observed increases in nicotine deliveries. The statistical chance that analytical variation could explain the results is vanishingly small. To begin with, the laboratory equipment used to measure nicotine and tar yields produces generally consistent results. The equipment has 20 ports, four of which are dedicated to measuring the tar and nicotine content of "monitor cigarettes" to guard against any "drifting" of the equipment.

Moreover, the trends reported by FDA from the FTC data reflect the results of literally tens of thousands of individual measurements of cigarettes. The reported tar and nicotine yield for any specific cigarette variety in a given year is the average of the test results of 100 individual cigarettes. The average tar and nicotine yields for all cigarette varieties in a given yield category, such as low-yield cigarettes, is the average of the

reported tar and nicotine yields for each cigarette variety in the category. Any analytical variation in the testing of individual cigarettes will have at most a very small effect on the averages reported from so large a sample size.

Fifth, the questions raised by the industry regarding the origin of the sales-weighted data are groundless. The data for 1984, 1985, and 1986 came from the FTC. Although the FTC may not have issued a report on tar and nicotine deliveries for each of those years, the FTC informed the Agency that it did nonetheless collect tar and nicotine data for these years. The 1991 and 1992 data do use information from slightly fewer brands than the brands listed in the FTC's published reports for those years; however, the explanation is that the FTC did not have tar, nicotine, and sales data for every single brand listed in the published reports. Only those brands for which data were missing were eliminated by the FTC in calculating the sales-weighted averages. The sales data used by the FTC to calculate the sales-weighted averages came from the tobacco manufacturers.

Finally, contrary to the industry's assertion, FDA did put the data and analysis it relied upon in the administrative record.[949]

Thus, contrary to the comments of the industry, FDA finds that a reasonable methodology was used to calculate nicotine deliveries.

3. Philip Morris asserts that it has few cigarettes with an enhanced nicotine/tar ratio of 0.10, compared to the naturally occurring ratio of 0.07. The company argues that this is evidence that it does not design its cigarettes to enhance nicotine deliveries. Philip Morris further asserts that two Philip Morris brands with nicotine/tar ratios of

[949] *See* Letter from Schultz WB (FDA), to Merrill R (Covington & Burling) (Dec. 27, 1995). *See* AR (Vol. 711 Ref. 7).

approximately 0.10 analyzed by Rep. Henry A. Waxman and cited by FDA (Merit Ultima and regular Benson & Hedges filtered cigarettes) do not reflect intentional nicotine manipulation.

The Agency disagrees that cigarettes with an elevated nicotine/tar ratio of 0.10 are uncommon. In 1995, for instance, over 90 varieties of cigarettes had a nicotine/tar ratio of 0.10 or higher.[950] Particularly among ultra-low-tar cigarettes, there are many examples of cigarettes with relatively enhanced nicotine deliveries and nicotine/tar ratios. Over 40% of cigarettes with tar deliveries of 5 mg or less have an enhanced nicotine/tar ratio of 0.10 or greater.[951] One example is the Merit Ultima, which is manufactured by Philip Morris and has a nicotine/tar ratio of 0.10.[952] Other examples are RJR's Winston Ultra Lights 100's and king-size Camel Ultra Lights, which have tar deliveries of 0.5 mg and nicotine deliveries of 0.5 mg, resulting in a nicotine/tar ratio of 0.10.[953] The deliveries of nicotine and tar in the Winston Ultra Lights 100's and the king-size Camel Ultra Lights are exactly the deliveries that RJR researchers recommended to produce "a low tar value" while "maintaining the nicotine as high as possible."[954] The existence of low-tar cigarettes with relatively elevated nicotine deliveries is compelling evidence that cigarette manufacturers design these cigarettes to provide enhanced nicotine deliveries.

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[950] Federal Trade Commission, *Report of "Tar," Nicotine, and Carbon Monoxide of the Smoke of 1107 Varieties of Domestic Cigarettes* (1995). *See* AR (Vol. 535 Ref. 96, vol. IV.B).

[951] *Id.*

[952] *Id.*

[953] *Id.*

[954] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 10. *See* AR (Vol. 700 Ref. 593).

II.C.6.

Moreover, even if no ultra-low-tar cigarettes had a nicotine/tar ratio of precisely 0.10, this would prove very little. As discussed in section II.C.3.a., Philip Morris' product development efforts concluded that "the optimum nicotine to tar . . . ratio for a [low-delivery] cigarette is *somewhat higher* than that occurring in smoke from the natural state of tobacco."[955] This research did not conclude that the "somewhat higher" ratio had to be a ratio of 0.10 (which is more than 40% higher than the "natural ratio" of 0.07) or greater. Consistent with Philip Morris' product development recommendations, most of the lowest-yield cigarettes do in fact have "somewhat higher" nicotine/tar ratios of 0.08 or greater. *See* Jurisdictional Analysis, 60 FR 41724.

The Agency rejects Philip Morris' claim that the enhanced nicotine/tar ratio of 0.10 in Merit Ultima can be explained by "the physics of low-yield filtration and ventilation."[956] FDA's own analysis has shown that the Merit Ultima uses a blend richer in nicotine than the blends used in either the Merit Filter 100's or the Merit Ultra Lights. See Jurisdictional Analysis, 60 FR 41723–41724. This deliberately chosen nicotine-rich blend contributes to the elevated nicotine/tar ratio in the Merit Ultima—apart from any effects of filtration or ventilation. *See* section II.C.4.a.ii. Moreover, to the extent that filtration and ventilation contribute to the elevated nicotine/tar ratio, this effect is the result of deliberate design decisions. *See* section II.C.4.b.

The Agency is also not persuaded that the enhanced nicotine/tar ratios in the regular Benson & Hedges filtered cigarettes can be dismissed as "minuscule variations" in

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[955] Jones B, Houck W, Martin P (Philip Morris Inc.), *Low Delivery Cigarettes and Increased Nicotine/Tar Ratios, A Replication* (Oct. 1975), in 141 Cong. Rec. H8132 (daily ed. Aug. 1, 1995) (emphasis added). *See* AR (Vol. 711 Ref. 6).

[956] Philip Morris Inc., Comment (Jan. 2, 1996), at 43. *See* AR (Vol. 519 Ref. 105).

tar and nicotine deliveries. A statistical analysis of the cigarettes prepared for and released by Rep. Waxman concluded that the possibility that the cigarette's enhanced nicotine/tar ratio could be explained by random fluctuations in tar and nicotine levels was virtually zero.[957]

iii. Comments on Chemical Manipulation.

1. Comments from the tobacco industry acknowledge that cigarette manufacturers add ammonia compounds to tobacco. However, the comments argue that the addition of ammonia does not have pharmacological significance because virtually all nicotine in cigarette smoke is absorbed into the bloodstream regardless of the pH of the smoke; because substantial amounts of ammonia would be required to raise smoke pH from 6.0 to 7.5 or 8.0; and because ammonia compounds do not increase the efficiency of the transfer of nicotine from the tobacco to the smoke.

The Agency disagrees with these comments. They conflict with the evidence from the cigarette industry documents in the record, as well as with basic scientific principles.

The evidence in the record demonstrates that the cigarette manufacturers add ammonia compounds to cigarettes to produce several pharmacological effects. As described in the industry documents, the pharmacologically significant effects of adding ammonia compounds to tobacco are (1) to increase the transfer of nicotine from the cigarette to the smoke; (2) to increase the rate of nicotine absorption in the mouth; and (3) possibly to increase the speed of nicotine absorption in the lungs. *See* section II.C.4.c.

[957] Statement of Waxman HA, 141 Cong. Rec. H8009 (daily ed. Jul. 31, 1995). *See* AR (Vol. 27 Ref. 376a).

Each of these three effects of adding ammonia compounds is significant even if the industry were correct that the lungs absorb virtually all of the nicotine that is inhaled.[958] The first effect—increasing the transfer of nicotine from the cigarette to the smoke—is significant because it increases the quantity of nicotine *delivered* to the lungs. Most of the nicotine in a cigarette never enters the mouth of a smoker. Rather, it is trapped in the filter; lost to the atmosphere; or destroyed or decomposed by the heat of the cigarette.[959] According to the statement of Dr. Farone, the former Philip Morris Director of Applied Research, however, the effect of adding ammonia compounds is "to deliver more of the available nicotine in the blend to the smoker."[960] Documents from the American Tobacco Company make a similar point, asserting that the use of alkaline compounds will "increas[e] the amount of nicotine that is transferred from the tobacco to the mainstream smoke."[961]

The second effect is likewise significant regardless of the efficiency of nicotine absorption in the lungs. This effect is to increase the amount of nicotine that the smoker

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[958] In fact, it is not clear that the lungs absorb virtually all the nicotine that is inhaled. According to one researcher, "[d]epending on inhalation patterns, retention times, and related factors, smokers may retain anywhere from 30% or less up to 90% or more of the total nicotine generated and delivered via the inhaled smoke." Huber GL, Physical, chemical, and biological properties of tobacco, cigarette smoke, and other tobacco products, *Seminars in Respiratory Medicine* 1989;10:297-332, at 304. *See* AR (Vol. 333 Ref. 5045).

[959] Armitage AK, Dollery CT, George CF, *et al.*, Absorption and metabolism of nicotine from cigarettes, *British Medical Journal*, 1975:313-316, at 315 ("[N]o more than 25% of the total nicotine content of the cigarette is likely to appear in the mainstream smoke. Most of the nicotine is lost into the surrounding air and sidestream smoke or is retained in the butt"). *See* AR (Vol. 131 Ref. 1462).

[960] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 13. *See* AR (Vol. 638 Ref. 2).

[961] Bodenhamer NL (American Tobacco), Leaf Services Monthly Report for June (Jun. 30, 1980). *See* AR (Vol. 27 Ref. 385).

absorbs through the *mouth*—not the lungs. Adding ammonia compounds raises the pH of the tobacco smoke. *See* section II.C.4.c. According to RJR researchers, by raising pH in a low-tar cigarette from just 6.0 to 6.5, "*you increase the nicotine transfer in the mouth.*"[962]

The third effect is a possible increase in the speed of nicotine absorption in the lungs. The increase in pH caused by the addition of ammonia compounds increases the proportion of "free" or "extractable" nicotine in the smoke. *See* section II.C.4.c. According to documents from BATCO, Brown & Williamson's parent company hypothesized that "with a higher 'extractable' nicotine, nicotine reaches the brain more quickly."[963] The BATCO researchers further postulate that "in human smoking a difference in the time of nicotine absorption of tenths of a second may be important."[964]

In light of this evidence from former cigarette industry employees and the industry's own documents, the industry's assertion that adding ammonia compounds has no pharmacological significance is not credible.

The tobacco industry comment also asserts that significant quantities of ammonia compounds are needed to raise the pH of smoke from 6.0 to 7.5 or 8.0. However, no scientific support is provided for this assertion. Moreover, even if the assertion were correct, it would be largely irrelevant. Significantly smaller increases in smoke pH are likely to have the pharmacological effects described above. As noted above, for instance,

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[962] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 7 (emphasis added). *See* AR (Vol. 700 Ref. 593).

[963] BATCO, *Further Work on 'Extractable' Nicotine*, Southampton, England (1966), at 7. *See* AR (Vol. 62 Ref. 308).

[964] *Id.* at 9.

documents from RJR conclude that simply increasing the pH of smoke from 6.0 to 6.5 is sufficient to increase the absorption of nicotine in the mouth.[965]

The Agency further disagrees with the tobacco industry comment that the pH of cigarette tobacco has no bearing on the efficiency of nicotine transfer from the tobacco to the smoke. It is a basic scientific principle that compounds in free or unbound forms are vaporized more readily than compounds bound together in salts.[966] Studies of cocaine, for instance, show that when cocaine is bound as a salt (as in cocaine hydrochloride), much of the cocaine is degraded during pyrolysis; in contrast, when the cocaine is converted to "free" form, the transfer of the cocaine to the smoke is much greater.[967] The tobacco industry comment provides no evidence to refute these basic scientific principles or to rebut the evidence in the record showing that the conversion of nicotine from its bound form to its free form increases the transfer of nicotine to smoke.[968]

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[965] Senkus M (R. J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 7 (emphasis added). *See* AR (Vol. 700 Ref. 593).

[966] Morrison RT, Boyd RN, *Organic Chemistry*, 2d ed., 1966, in Barnett G, Chiang CN eds., *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs*, A Research Monograph, Biomedical Publications, 2d edition, 1985, at 26. *See* AR (Vol. 711 Ref. 19).

[967] Cook CE, Jeffcoat AR, Perez-Reyes M, Pharmacokinetic studies of cocaine and phencyclidine in man, in Barnett G, Chiang CN eds., *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs, A Research Monograph*, Biomedical Publications, 2d edition, 1985, at 64-65. *See* AR (Vol. 711 Ref. 16).

[968] After the close of the comment period, FDA received a series of RJR documents from the 1970's regarding the effect of pH adjustments on nicotine delivery. These documents had been made public in a lawsuit involving RJR. Although not necessary to FDA's analysis, these documents provide further confirmation that cigarette manufacturers raise the pH of cigarette smoke to increase the amount of "free nicotine" that is delivered to the smoker, and that this increase in "free nicotine" has a pharmacological effect. One of these documents describes RJR's finding that the pH level of Marlboro and Kool cigarettes had risen significantly, with corresponding increases in "free" nicotine deliveries, and in sales. Teague CE (RJR), *Implications and Activities Arising from Correlation of Smoke pH with Nicotine Impact, Other Smoke Qualities, and Cigarette Sales*, at 1-3. *See* AR (Vol. 711 Ref. 47). The document states:

> In essence, a cigarette is a system for delivery of nicotine to the smoker in attractive, useful form. At "normal" smoke pH, at or below about 6.0, essentially all of the smoke nicotine is chemically combined with acidic